

# Corneal topographic alterations in women with endometriosis: data analysis in an ophthalmologic clinic

Alterações topográficas corneanas em mulheres portadoras de endometriose: análise de dados em uma clínica oftalmológica

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## ABSTRACT

**Objective:** To verify whether there are pathological dysfunctions in the cornea of patients with endometriosis.

**Methods:** Case-control research with a quantitative approach that compared topographic and tomographic examinations of the cornea of patients with a laparoscopic diagnosis of endometriosis, without the use of hormonal medications, to the control group.

**Results:** We analyzed 78 eyes, 34 from the endometriosis group and 44 from the control group. The loss of orthogonality between the axes of the corneal curvatures was more frequent in the group with endometriosis ( $p = 0.0744$ ). The difference between the mean keratometric measurements of the two eyes was significantly greater in the control group ( $p = 0.0204$ ). In the tomographic findings, the group with endometriosis presented higher means of posterior elevation compared to the control group ( $p = 0.0060$ ).

**Conclusion:** The results do not allow us to conclude that women with endometriosis have a higher risk of developing corneal ectasia, although the posterior elevation map demonstrated a greater posterior curvature of the cornea in this group, with a statistically significant difference. However, an isolated increase in the posterior elevation map does not have good diagnostic accuracy.

## RESUMO

**Objetivo:** Verificar se há disfunções patológicas na córnea de pacientes portadoras de endometriose.

**Métodos:** Pesquisa do tipo caso-controle de abordagem quantitativa, que comparou exames topográficos e tomográficos da córnea de pacientes com diagnóstico laparoscópico de endometriose, sem uso de medicações hormonais, ao grupo controle.

**Resultados:** Foram analisados 78 olhos, 34 do grupo com endometriose e 44 do grupo controle. A perda da ortogonalidade entre os eixos das curvaturas corneanas foi mais frequente no grupo com endometriose ( $p = 0,0744$ ). A diferença entre as médias das medidas ceratométricas dos dois olhos foi significativamente maior no grupo controle ( $p = 0,0204$ ). Nos achados tomográficos, o grupo com endometriose apresentou maiores médias de elevação posterior em relação ao controle ( $p = 0,0060$ ).

**Conclusão:** Os resultados não permitem concluir que portadoras de endometriose têm maior risco de desenvolver ectasia corneana, embora o mapa de elevação posterior tenha demonstrado maior curvatura posterior da córnea nesse grupo, com diferença estatisticamente significativa. Contudo, um aumento isolado no mapa de elevação posterior não possui boa acurácia diagnóstica.

## INTRODUCTION

Cornea is a transparent, avascular and richly innervated structure that covers the front portion of the eye and is responsible for approximately 75% of visual refraction.<sup>(1,2)</sup> Corneal ectasias, such as keratoconus, pellucid marginal degeneration, and keratoglobus, are characterized, according to the Global Consensus on Keratoconus (2015), by progressive thinning and/or protrusion of the cornea due to an etiopathogenesis that is still uncertain. This topic deserves to be highlighted, since ectasias are becoming more frequent in the world population and are related to decreased visual acuity, increased deformations of the eyeball and significant ocular morbidity.<sup>(3)</sup>

Furthermore, recent assumptions of an association between ectasia and increased levels of female sex hormones have aroused scientific curiosity, generating a need for studies to prove such theories.<sup>(4)</sup> In this sense, studies have found the presence of sexual hormone receptors, including estrogen, progesterone, and androgens in human corneas, establishing a surprising relationship between corneal and gonadotropic activity, raising the possibility of a relationship between ophthalmological changes and pathologies that involve changes in the hormonal levels, such as menopause, pregnancy, endometriosis, among others.<sup>(5-7)</sup>

Likewise, it is known that a marked increase in estradiol levels can stimulate pro-inflammatory cytokines present in human corneal epithelial cells, associated with keratoconus and other ectatic diseases.<sup>(8)</sup> Furthermore, research has shown that men with keratoconus have increased estradiol levels, as well as that estrogen supplementation in patients with keratoconus resulted in the progression of the disease in all eyes evaluated.<sup>(9,10)</sup> In this sense, a case of late progression of keratoconus after initiating therapy with the estrogen activity regulator with tibolone was reported.<sup>(11)</sup> Consequently, the cornea is sensitive to estrogen and the functionality of its cells can be influenced by hormonal changes.

Thus, considering that endometriosis has a high incidence in Brazil and its pathogenesis is associated with an increase in circulating estradiol values, through the analysis of corneal topography and tomography exams, the present research fits the objective of verifying whether there are pathological dysfunctions in the cornea of patients with endometriosis.

## METHODS

This was case-control research with a quantitative approach that analyzed corneal tomography and

topography data collected using the Pentacam Oculyzer (Oculus, Wetzlar, Germany) and the Topolyzer (Oculus, Wetzlar, Germany), respectively, in 34 eyes of 17 women with a previous laparoscopic diagnosis of endometriosis and 44 eyes of 22 previously healthy women who made up the control group.

The study began after approval of the research project by the Ethics Committee of the institution in charge, enabling data collection between January 2023 and April 2023. The study population included patients from a private gynecology and obstetrics clinic, located in Joaçaba (SC), as well as a control group. In this scenario, patients with a history of laparoscopy and a positive anatomopathological pathology for endometriosis, without the use of hormonal medications to control pain, were contacted individually, and were then subjected to corneal topography and tomography exams, after a brief explanation of the content of the research, and after signing the Free and Informed Consent Form (ICF) and the Image Use Acceptance Term.

The control group was made up of previously healthy women, without previous ophthalmological disease and without endometriosis, with an age similar to the mean standard deviation found in the other group studied. To this end, the ophthalmology clinic carried out a retrospective analysis of the medical records of patients who were candidates for refractive surgery and who had already undergone tomography and corneal topography exams, selecting only those who stated, during a previous anamnesis, that they had no previous illnesses.

Patients who were menopausal, were taking hormonal medications, were pregnant or breastfeeding during data collection, or had a history of refractive eye surgery (laser-assisted-in-situ-keratomileusis [LASIK] and photorefractive keratectomy [PRK]), were excluded, as well as those who had already diagnosed eye disease or were on continuous use of eye drops. All test results were analyzed by the same ophthalmologist.

Numerical variables were compared using an unpaired T test. Categorical variables, such as those observed in the presence or absence of orthogonality, were analyzed using Fisher's exact test. The data were analyzed using the Python 3.9 language, using the SciPy-Stats statistical library. The descriptive level  $p < 0.05$  was adopted.

## RESULTS

The mean ages of the participants were  $35.12 \pm 6.76$  years for the control group and  $31.73 \pm 5.24$  years for the endometriosis group. All were female and met the study's inclusion criteria.

The topographic results are shown in table 1 and figure 1. Only the keratometric difference variable showed significant distinction. The control group showed a significantly greater keratometric difference compared to the endometriosis group ( $t = 2.42$ ;  $fd = 37$ ;  $p = 0.0204$ ).

**Table 1.** Topographic findings between participants who had endometriosis and the control group. For numerical variables, data were analyzed using the *t* test and categorical variables using Fisher's exact test

Variable	Endometriosis	Control	p-value
Age	35.12 ± 6.76	31.73 ± 5.24	0.0859
K1	42.98 ± 1.47	43.2 ± 1.4	0.5005
K2	44.03 ± 1.79	44.72 ± 1.19	0.4320
Maximum K	44.78 ± 1.7	45.4 ± 1.3	0.0728
I-S Index	0.17 ± 0.41	0.03 ± 0.575	0.2176
Orthogonality			0.0744
Yes	28 (82.35%)	44 (100%)	
No	6 (17.65%)	0	
Difference of the keratometric average between the eyes	0.22 ± 0.15	0.46 ± 0.38	0.0204*

Maximum K: maximum keratometry. Orthogonality: orthogonality between the k1 and k2 axes.

\*  $p < 0.05$  between groups.

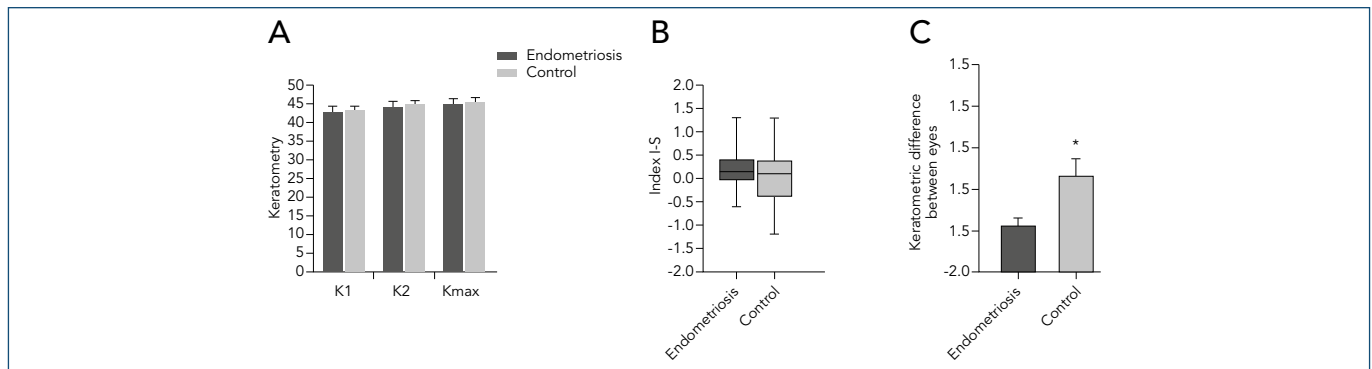
K1: lowest keratometric average; K2: highest keratometric average.

Fisher's exact test revealed an almost significant difference in the frequency of orthogonality between the groups ( $p = 0.0744$ ), with a higher prevalence of changes in the endometriosis group.

The data from the tomographic examination are presented in table 2 and figure 2, which showed a statistically significant difference only in the posterior elevation parameter; the endometriosis group presented higher means in this variable ( $t = 2.87$ ;  $fd = 76$ ;  $p = 0.0060$ ), compared to the control group, with a measure of 9  $\mu\text{m}$  of difference between the samples.

**Table 2.** Tomographic findings between participants who had endometriosis and the control group. For numerical variables, data were analyzed using the *t* test

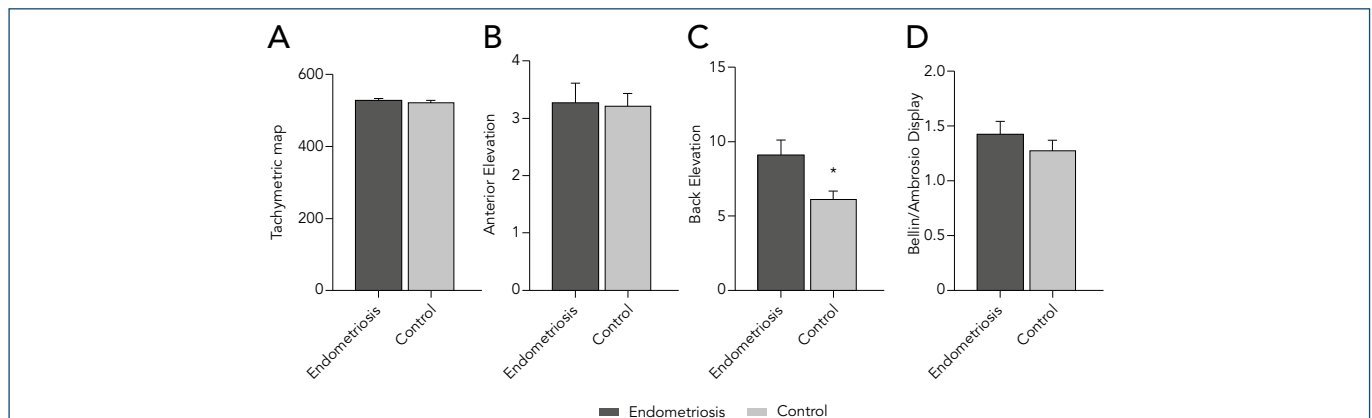
Variable	Endometriosis	Control	p-value
Tachymetric map	529.4 ± 2.3	522.9 ± 35.2	0.3702
Anterior elevation	3.26 ± 2.1	3.2 ± 1.4	0.8794
Posterior elevation	9.11 ± 5.7	6.14 ± 3.6	0.0060
Bellin/Ambrósio -D	0.43 ± 0.6	1.3 ± 0.6	0.3147



\*  $p < 0.05$  between groups.

K1: lowest keratometric average; K2: highest keratometric average.

**Figure 1.** Comparison of topographic ophthalmological variables relative to: (A) mean and standard error of the keratometry mean; (B) boxplot of the I-S Index and (C) mean and standard error of the difference in the keratometry mean of the endometriosis and control groups.



\*  $p < 0.05$  between groups.

**Figure 2.** Comparisons of tomographic ophthalmological variables relating to: (A) mean and standard error of the pachymetric map (B) mean and standard error of elevation and (C) posterior; (D) mean and standard error of the Bellin/Ambrósio Display mean for the endometriosis and control groups.

## DISCUSSION

The gold standard for endometriosis is exploratory laparoscopy with a positive result, since this disease has a variable clinical course that can be confused with other gynecological conditions, which often cannot be differentiated by imaging tests.<sup>(12,13)</sup> That is why this inclusion criterion was used in this research. The patients included in the research were not taking hormonal medication, which allows endometriosis to be analyzed without the possible interference of hormonal therapies.

Endometriosis foci grow due to the hormonal action of estrogen, which is why the disease is called estrogen dependent.<sup>(14)</sup> Exposure to estrogen in porcine corneas caused an increase in thickness and a decrease in rigidity, leading to the belief that hormonal exposure may be a risk factor for corneal ectasia.<sup>(7)</sup> Variations in some biomechanical parameters of the cornea may appear during the ovulation period, a phase in which there is an increase in estrogen, compared to the rest of the menstrual cycle of the same patient.<sup>(15)</sup> However, although blood levels of estrogen and progesterone influenced the increase in intraocular pressure, estrogen and progesterone did not consistently modify the topography or biomechanical properties of healthy corneas.<sup>(16)</sup>

In the present research, it was noted that only the difference between the average keratometric measurements of the two eyes showed a significant difference. The control group showed a significantly greater difference between the mean keratometric measurements of the two eyes compared to the endometriosis group ( $t = 2.42$ ;  $fd = 37$ ;  $p = 0.0204$ ). Fisher's exact test revealed an almost significant difference in the frequency of orthogonality between the groups ( $p = 0.0744$ ), with a higher prevalence of changes in the endometriosis group.

The Placido rings corneal topography presents some relevant indices for detecting keratoconus: Central K (central curvature); I-S values (inferior-superior dioptric asymmetry); and SRAX (relative inclination of the steepest radial axes above and below the horizontal meridian). In these parameters, a central K greater than 47.20 D, I-S index greater than 1.2 and the SRAX index above 21° identified 98% of patients with KC.<sup>(17)</sup> Different curvatures between the two eyes can also be an indication of corneal disease.

The I-S index has a strong relationship with the diagnosis of corneal ectasia, especially at values above 1.2.<sup>(18)</sup> In this context, the mean I-S indexes of the endometriosis group ( $0.17 \pm 0.41$ ) were higher than the mean I-S indexes of the control group ( $0.03 \pm 0.575$ ), this difference being

not statistically significant ( $p = 0.2176$ ). Therefore, it is not possible to confirm a concrete relationship between the I-S index and endometriosis; however, we observed a slight increase in the averages in this group, which can be considered a risk factor for the development of corneal ectasia.

The use of tomography (Pentacam) increases the specificity and sensitivity to differentiate normal corneas from those that are diseased and susceptible to ectasia.<sup>(19)</sup> There are reports in the literature that demonstrate patients with topography exams within normal parameters, but changes in the tomographic exam, demonstrating an earlier detection of corneal diseases.<sup>(20)</sup>

Therefore, a tomographic examination was also carried out, with the data represented in table 2, which showed a statistical difference only in the posterior elevation parameter, with the endometriosis group presenting higher means in this variable ( $t = 2.87$ ;  $fd = 76$ ;  $p = 0.0060$ ), compared to the control group, with a difference of 9  $\mu\text{m}$  between the samples.

Studies demonstrate that the radius of posterior corneal curvature makes it possible to detect corneal disease in its earliest phase, compared to topography<sup>(17,21)</sup>. It is known that posterior elevation of the cornea is an early sign of keratoconus; therefore, this parameter should always be evaluated, especially during refractive surgeries, to avoid post-LASIK corneal ectasia.<sup>(22)</sup>

In relation to the Belin/Ambrosio Enhanced Display (BAD) index, the ideal cutoff point to differentiate keratoconus from normal eyes would be 1.6.<sup>(23)</sup> This parameter was slightly increased in the group of patients with endometriosis, but not significantly ( $p = 0.3147$ ). There was no statistically significant difference in the other tomographic parameters analyzed.

Finally, it is worth highlighting that keratoconus is diagnosed based on a set of clinical signs, such as: Munson sign, which is the protrusion of the lower eyelid when looking down, and decreased vision, in addition to aspects considered by the ABCD of Belin: (A) the radius of the anterior corneal curvature; (B) the radius of the posterior corneal curvature; (C) corneal pachymetry at the thinnest point; and (D) visual acuity. Therefore, the change in an isolated parameter in such exams does not constitute a diagnosis of corneal ectasia, requiring a set of factors to improve diagnostic accuracy.<sup>(17)</sup>

## CONCLUSION

Although the cornea carries sex hormone receptors and can therefore be affected by systemic diseases that involve changes in the levels of circulating sex hormones, based

on the sample studied, it cannot be said that the presence of endometriosis confirmed by surgery is a predisposing factor of corneal ectasia.

However, among all the data that generate suspicion for corneal disease, there was a statistically significant difference in the posterior elevation map of those with endometriosis. It is known that increased posterior curvature of the cornea is an early sign of keratoconus, but that just one altered parameter alone does not have good diagnostic accuracy. This study had the limitation of a small sample and still scarce literature regarding this probable relationship between endometriosis and corneal ectasia.

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